REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application. With this amendment, Claims 36-37 and 41-43 have been canceled without prejudice, Claims 28-35, 38-39 and 44 have been amended to clarify what Applicants have always regarded as their invention and new Claims 48-52 have been added. The support for the new claims can be found at least in Example 142, Assay 34, starting on page 493, line 10 of the specification.

Claims 28-35, 38-40 and 44-52 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Priority

According to the Examiner, "the claimed polypeptide (PRO1304, SEQ ID NO:180) having utility in fetal hemoglobin induction (Assay 107, page 511) has earliest priority to February 18, 2000 as disclosed in PCT/US/04342."

Applicants rely on the fetal hemoglobin induction in an erythroblastic cell line assay (Example 147, Assay 107) for support of patentable utility. This data was first disclosed in International Application Serial No. PCT/US00/04342 filed on February 18, 2000, the priority of which is claimed in the present application. Accordingly, the present application is entitled to at least the February 18, 2000 priority for subject matter defined in Claims 28-35, 38-40 and 44-47. Applicants respectfully submit that drugs increasing fetal hemoglobin levels are, for example, useful in the treatment of beta-chain hemoglobinopathies such as sickle cell disease (SCD) and Cooley's anemia (beta-thalassemia). It is well established that SCD and CA can be cured with adequate reactivation of endogenous fetal hemoglobin genes silenced during development.

Applicants further rely on the induction of c-fos in endothelial cells (Example 142, Assay 34) for support of patentable utility. The data was first disclosed in International Application Serial No. PCT/US99/28313 filed on November 30, 1999, the priority of which is claimed in the present application. In support, Applicants enclose herewith pages 174-175 of the

PCT Publication WO 0032221, corresponding to PCT Application PCT/US99/28313. Accordingly, the present application is entitled to at least the November 30, 1999 priority for subject matter defined in Claims 33-35, 38-40 and 44-52.

Further, the PRO polypeptide sequence and its encoding nucleic acid sequence were first disclosed in the U.S. Provisional Application No. 60/100,711, filed on September 17, 1998, priority to which has been claimed in this application.

Claim Objections

Claims 28-33, 38-39, and 41 are objected to for reciting "the nucleic acid sequence shown in Figure 103 (SEQ ID NO:179)" and "the full-length coding sequence of the nucleic acid sequence shown in Figure 103 (SEQ ID NO:179)" as steps "e" and "f", because stems "e" and "f" are not patentably distinct.

Applicants respectfully disagree and traverse the rejection.

Step "e" recites "the nucleic acid sequence shown in Figure 103 (SEQ ID NO:179)", hence the claim comprises the entire length of SEQ ID NO:179. On the other hand, step "f" recites "the full-length coding sequence of the nucleic acid sequence shown in Figure 103 (SEQ ID NO:179)". Therefore, step "f" comprises only the coding sequence of the SEQ ID NO:179 and not the entire sequence of the SEQ ID NO:179. It is well understood in the art that a coding sequence begins at a start codon, "ATG", and ends at a stop codon, such as "TAG". The start and stop codons are underlined and clearly marked in Figure 103 (SEQ ID NO:179). Therefore, Applicants respectfully submit that steps "e" and "f" are patentably distinct.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present objection.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claim 42 is rejected under 35 U.S.C. §112, second paragraph, allegedly because the term "stringent conditions" are not defined by the claim.

Without acquiescing to these rejections, Applicants submit that the cancellation of Claims 41-43 renders the rejection of these claims (and, as a consequence, those claims

dependent from the same) moot. Accordingly, Applicants request that the rejection of Claim 42 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner noted that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

In particular, the Examiner notes that "[t]he claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity" with SEQ ID NO:180, but "the claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature." The Examiner further asserts that "the specification fails to provide a written description of the amino acid sequences within SEQ ID NO:180 that form the extracellular domain and to isolated nucleic acids that hybridize to nucleic acid sequences that encode the polypeptide of SEQ ID NO:180." Applicants respectfully submit that the pending claims of instant application are drawn to polynucleotides and not polypeptides.

Applicants submit that the cancellation of Claims 36-37 and 41-43 renders the rejection of these claims moot.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit that amended Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation that the encoded polypeptide "has fetal hemoglobin inducing activity." Accordingly, it is no longer true that the claims are drawn to a genus of polynucleotides defined by sequence identity alone. Furthermore, as amended, Claims 28-33 (and, as a consequence, those claims dependent from the same) no longer recite the term "extracellular domain." Therefore, the recited biological activity, coupled with a well defined, and relatively high degree of sequence identity is believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this

application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §102

Claims 28-37 and 41-47 are rejected under 35 U.S.C. §102(e) as being anticipated by Young *et al.* (U.S. Patent No. 6,525,174, filling date December 4, 1998). Applicants would like to thank the Examiner for telephone conference on October 7, 2004 for confirming that the effective priority date of the U.S. Patent No. 6,525,174 is December 4, 1998. The Examiner alleges that Young teaches "an isolated nucleic acid sequence encoding a polypeptide that is 100% identical to SEQ ID NO:180." However, Applicants respectfully submit that the nucleic acid sequence or the polypeptide sequence of Young is not 100% identical to the SEQ ID NO:179 or SEQ ID NO:180 of the present application. This is indirectly acknowledged by the fact that the Examiner noted that the protein sequence of Young is 98.1% identical to SEQ ID NO:180 in parallel application U.S. Patent Application No. 10/006,117.

Applicants submit that the cancellation of Claims 36-37 and 41-43 renders the rejection of these claims moot.

Applicants have claimed priority to U.S. Provisional Application No. 60/100,711, filed on September 17, 1998. The present application is entitled to the priority date of September 17, 1998, which precedes, at least by two months, the earliest priority date of Young *et al.* (December 4, 1998). Accordingly, Young *et al.* is not prior art against the present application and Claims 28-35 and 44-47 are patentable.

Further, Applicants respectfully submit Declaration under 37 C.F.R. §1.131 by Dr. Eaton, Dr. Goddard, Dr. Godowski, Dr. Gurney, Dr. Williams and Dr. Wood that establishes that Applicants had cloned, sequenced and homology to FK-506 binding protein identified before the prior art date of December 4, 1998. The consideration of the Declaration is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

U.S. Provisional Application No. 60/100,711 simply needs to disclose what is disclosed in the cited reference to support the priority claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(e) rejection over Young *et al.*, the Declaration by Dr. Eaton, Dr. Goddard, Dr. Godowski, Dr. Gurney, Dr. Williams and Dr. Wood ("Declaration") simply needs to provide a disclosure commensurate in scope with the disclosure in the prior art document by Young *et al.* to support the priority claim.

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. §1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet

established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

Young *et al.* discloses a nucleic acid sequence encoding a polypeptide having homology with the FK506-binding protein family. (See US Patent No. 6,525,174, column 26 lines 60-63). Accordingly, since Young only discloses a polypeptide sequence, its encoding nucleic acid sequence and a sequence homology, Applicants respectfully submit that the Declaration simply needs to show possession of the polypeptide sequence, its encoding polynucleotide sequence as disclosed in Young, and a sequence homology in order to overcome the 35 U.S.C. §102 rejection.

Applicants respectfully submit that U.S. Provisional Application No. 60/100,711, filed on September 17, 1998, provides the nucleic acid and amino acid sequences of the PRO1304 polypeptide and the homology of the polypeptide with the FK-506 binding protein (see U.S. Provisional Application No. 60/100,711 on page 12, under the section titled "Full-length PRO1304 Polypeptide"). Considering its homology to the FK-506 binding protein, Applicants further suggest the PRO1304 polypeptide to be newly identified member of the FK506 binding protein family and may possess activity typical of that family.

The Declaration clearly states that U.S. Provisional Application No. 60/100,711, filed on September 17, 1998, discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:2, which are identical to SEQ ID NO:179 and SEQ ID NO:180, respectively, of the above-identified

application. Further, the Declaration confirms that U.S. Provisional Application No. 60/100,711, filed on September 17, 1998, discloses that SEQ ID NO:2, corresponding to SEQ ID NO: 180 of the above-identified application, has homology to the FK506 binding protein.

Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that U.S. Provisional Application No. 60/100,711, filed on September 17, 1998, discloses all that the cited prior art discloses.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Applicants respectfully submit that Young *et al.* is not prior art under 102(e) since its effective priority date is after the invention by the Applicants for patent. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 28-35 and 44-47 under 35 U.S.C. §102(e).

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C50**)

Respectfully submitted,

Date: October 20, 2004 By: _____

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EXAMPLE 57

Induction of c-fos in Endothelial Cells

This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in endothelial cells.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO3, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of $1x10^4$ cells/well. The day after plating, the cells were starved by removing the growth media and treating the cells with 100 μl/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). The cells were incubated for 30 minutes at 37°C, in 5% CO_2. The samples were removed, and the first part of the bDNA kit protocol (Chiron Diagnostics, cat. #6005-037) was followed, where each capitalized reagent/buffer listed below was available from the kit.

Briefly, the amounts of the TM Lysis Buffer and Probes needed for the tests were calculated based on information provided by the manufacturer. The appropriate amounts of thawed Probes were added to the TM Lysis Buffer. The Capture Hybridization Buffer was warmed to room temperature. The bDNA strips were set up in the metal strip holders, and 100 μl of Capture Hybridization Buffer was added to each b-DNA well needed, followed by incubation for at least 30 minutes. The test plates with the cells were removed from the incubator, and the media was gently removed using the vacuum manifold. 100 μl of Lysis Hybridization Buffer with Probes were quickly pipetted into each well of the microtiter plates. The plates were then incubated at 55°C for 15 minutes. Upon removal from the incubator, the plates were placed on the vortex mixer with the microtiter adapter head and vortexed on the #2 setting for one minute. 80 μl of the lysate was removed and added to the bDNA wells containing the Capture Hybridization Buffer, and pipetted up and down to mix. The plates were incubated at 53°C for at least 16 hours.

On the next day, the second part of the bDNA kit protocol was followed. Specifically, the plates were removed from the incubator and placed on the bench to cool for 10 minutes. The volumes of additions needed were calculated based upon information provided by the manufacturer. An Amplifier Working Solution was prepared by making a 1:100 dilution of the Amplifier Concentrate (20 fm/μl) in AL Hybridization Buffer. The hybridization mixture was removed from the plates and washed twice with Wash A. 50 μl of Amplifier Working Solution was added to each well and the wells were incubated at 53°C for 30 minutes. The plates were then removed from the incubator and allowed to cool for 10 minutes. The Label Probe Working Solution was prepared by making a 1:100 dilution of Label Concentrate (40 pmoles/μl) in AL Hybridization Buffer. After the 10-minute cool-down period, the amplifier hybridization mixture was removed and the plates were washed twice with Wash A. 50 μl of Label Probe Working Solution was added to each well and the wells were incubated at 53°C for 15 minutes. After cooling for 10 minutes, the Substrate was warmed to room temperature. Upon addition of 3 μl of Substrate Enhancer to each ml of Substrate needed for the assay, the plates were allowed to cool for 10 minutes, the label hybridization mixture was removed. and the plates were washed twice with Wash A and three times with Wash D. 50 μl of the Substrate Solution with Enhancer was added to each well. The plates were incubated for 30 minutes

at 37°C and RLU was read in an appropriate luminometer.

The replicates were averaged and the coefficient of variation was determined. The measure of activity of the fold increase over the negative control (Protein 32/HEPES buffer described above) value was indicated by chemiluminescence units (RLU). The results are shown in TABLE 8 below, and are considered positive if the PRO polypeptide exhibits at least a two-fold value over the negative buffer control. Negative control = 1.00 RLU at 1.00% dilution. Positive control = 8.39 RLU at 1.00% dilution.